UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

November 28, 2001

SUBJECT: **Urea (Carbamide):** HED Science Assessment for Tolerance Reassessment Eligibility Decision (TRED) for the Frost Protectant Pesticide, Urea.

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Attached is the Health Effects Division's (HED's) science assessment supporting issuance of a Tolerance Reassessment Eligibility Decision (TRED) for urea. This document updates the tolerance exemption for this active ingredient issued by EPA in 1995. Supporting documents for the Urea TRED include:

- Toxicology Chapter of the TRED for the Pesticide, Urea. M. Centra (10/2/01)
- Tier 1 Drinking Water Estimated Environmental Concentrations for Urea. I Abdel-Saheb (10/11/01)

1. EXECUTIVE SUMMARY

1.1 Purpose

In 1995, the EPA granted a permanent exemption from the requirement of a tolerance for residues of the frost protectant urea in or on various raw agricultural commodities. Since this decision was made prior to the passage of the Food Quality Protection Act (FQPA, 1996), a revised hazard characterization that includes special sensitivity to infants and children is required for the urea Tolerance Reassessment Eligibility Decision (TRED) document.

1.2 Use Profile

Urea was registered by EPA in1995 for use as a frost protectant pesticide under the trade name Enfrost. Enfrost is a 43% liquid formulation of urea that can be applied commercially to a wide variety of field crops, vegetables, fruit trees and ornamentals to reduce frost damage. There are currently no residential uses for urea as a pesticide product. Enfrost is the only currently registered pesticide product containing urea as an active ingredient. Enfrost provides frost protection by modifying the protein produced by ice-nucleating bacteria. In addition to its use as frost protectant, several million tons of urea are produced annually for use in fertilizer and as an animal feed supplement. Urea is also use in the manufacture of dyes, fire retardant paints, plastisizers, and stabilizers for explosives.

1.3 Regulatory History

The active ingredient, urea, was affirmed to be Generally Recognized as Safe (GRAS) as a direct food ingredient by the Food and Drug Administration (FDA) in 1983 (21 Code of Federal Regulations (CFR) §184.1923). EPA has also listed urea as an inert ingredient exempted from the requirement of a tolerance when applied (as an inert or occasionally active ingredient) in pesticide formulations to: 1) growing crops or raw agricultural commodities after harvest as a stabilizer/inhibitor (40 CFR §180.1001(c)); 2) growing crops only as an adjuvant/intensifier for herbicides (40 CFR §180.1001(d)); or 3) animals as a stabilizer/inhibitor (40 CFR §180.1001(e)). Under §180.1001(a), an exemption from tolerance is granted when it appears that the total quantity of the pesticide or chemical in or on all raw agricultural commodities for which it is useful under current or proposed conditions of use will involve no hazard to the public health.

In 1995, in response to a request from Unocal Corp., EPA established a permanent exemption from the requirement of a tolerance for residues of urea used as a frost protectant in or on various agricultural commodities (40 CFR § 180.1117). EPA's tolerance exemption for the frost protectant urea was based on the following considerations. The primary basis was a series of toxicity studies performed on the product "Enfrost" which contains 43% urea; a review of these studies indicated that the product has a low toxicity to animals when administered via oral, dermal and inhalation routes of

exposure. EPA also cited previous regulatory actions to substantiate its decision, including FDA's designation of urea as a GRAS food ingredient and EPA's listing of urea as an inert ingredient in certain pesticide formulations with urea concentrations similar to those in the frost protectant. Finally, the Agency cited the natural occurrence of urea in crops and plants and in human and animal tissues and body fluids (humans excrete about 25 grams per day) as further basis for granting a tolerance exemption.

The 1995 rule established an exemption from the requirement of a tolerance for residues of urea when used before harvest as a frost protectant in or on the following raw agricultural commodities: alfalfa, almonds, apples, apricots, artichokes, asparagus, avocados, beans, bell peppers, blackberries, blueberries, broccoli, Brussels sprouts, boysenberries, caneberries, canola, cantaloupe, carrots, cauliflower, casaba, celery, cherries, chili peppers, Chinese cabbage (bok choy, napa), cooking peppers, corn, cotton, crenshaw, cucumbers, figs, grapefruit, grapes, honeydew melon, hops, kiwifruit, kohlrabi, lemons, lentils, lettuce, limes, macadamia nuts, musk melon, nectarines, olives, onions, oranges, peaches, pears, peanuts, peas, persian melon, pistachios, plums, potatoes, pumpkin, prunes, radish, raspberries, rice, safflower, sorghum, spinach, spinach (New Zealand), squash (winter and summer), strawberries, sugar beets, sunflower, sweet pepper, table beets, tangerines, tomatoes, walnuts, watermelon, and zucchini.

Enfrost was transferred from Unocal Corp to the Entek Corporation in 1995. Enfrost has not been actively produced or sold by Entek since the company acquired the registration for the product in 1995. However, Entek wishes to maintain active registration of Enfrost for potential future production and use. Therefore, as required by FQPA, EPA is now reassessing the 1995 exemption to determine whether infants and children exhibit enhanced sensitivity from exposure to the frost protectant urea..

1.4 Summary of Science Assessment Findings

From the available animal studies and human exposure data, HED has concluded that urea exhibits a low toxicity and exposures to urea used as a frost protectant present no unreasonable adverse human health effects. HED's analysis of extensive toxicology data in numerous species, including man, supports the 1995 decision to grant a permanent exemption from the requirement of a tolerance for residues of the frost protectant when used before harvest in the production of the raw agricultural commodities. Regarding FQPA, the data provide no indication of increased sensitivity of infants and children from exposure to urea. Therefore, the FQPA 10x factor to account for enhanced sensitivity of infants and children can be removed.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Chemical Name: Carbamide
Chemical Structure:

Empirical Formula:	$CO(NH_2)_2$
Molecular Weight:	60.66
Cas Registry No.:	57-13-6
PC Code:	084701
Trade Name:	Enfrost

Technical urea, $CO(NH_2)_2$ is the diamide of cargonic acid. It is a white, odorless, hygroscopic, crystalline solid with a melting point of 134-136 C and a density of 1.12 g/mL at 20 C. It is stable in the pure solid form and slowly hydrolyzes in water solutions to form carbon dioxide and ammonia. On standing, it may gradually develop a slight ammoniacal odor. Urea is highly soluble in water, glycerol and hot alcohol, but almost insoluble in chloroform and ether.

3.0 HAZARD CHARACTERIZATION

With the exception of six acute toxicity studies submitted by the registrant for the Enfrost formulation, the urea toxicity data base is comprised of the available literature data. These data are considered by HED's Toxicology Science Advisory Committee (TOX SAC) to be sufficient to assess the potential hazard to humans, including special sensitivity of infants and children. (D274740, M. Centra, 10/2/01)

3.1 Hazard Profile

3.1.1 Acute Toxicity

The six acute toxicological studies submitted by the registrant were performed on the end-use product "Enfrost" which contains 43.5% urea. Acute toxicity data from these studies are presented in Table I. A review of these data indicates that the frost protectant has a low toxicity to animals when administered via the oral, dermal or inhalation routes of exposure (Toxicity Categories III and IV). The lethal dose (LD_{50}) for an oral exposure in rats was 14,500 mg/kg which would be equivalent to a two pound ingestion of urea by an average size adult human. The acute toxicity of urea has also been evaluated in rabbits, cattle, sheep, dogs, and guinea pigs by oral, subcutaneous and intravenous exposures.

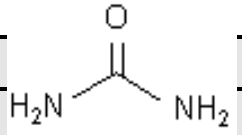

TABLE 1. ACUTE TOXICITY PROFILE FOR ENFROST (Urea, 43% a.i.)				
Guideline	**Study Type (Date)**	**MRID**	**Results**	**Tox.Cat.**
870.1100	Acute Oral-Rat (5/11/88)	40733304	$LD_{50} > 5000$ *mg/kg*	IV
870.1200	Acute Dermal-Rabbit (5/11/88)	40733305	$LD_{50} > 2000$ mg/kg	III

870.1300	Acute Inhalation-Rat (5/11/88)	40733301	LC_{50} > 4.8 mg/L	III
870.2400	Primary Eye Irritation-Rabbit (5/11/88)	40733302	Slight eye irritant	IV
870.2500	Primary Dermal irritation-Rabbit (5/11/88)	40733306	Slight dermal irritant	IV
870.2600	Dermal Sensitization-Guinea pig (5/11/88)	40733303	Non sensitizer	N/A

3.1.2 Data Waivers for Additional Toxicological Studies

In 1989 EPA granted data waivers for submission of additional toxicity studies for the use of urea as a frost protectant on food crops (Memoranda: Ritter to Wilson, dated 2/23/89 and Stolzenberg to Rossi, dated 6/13/89). HED's TOX SAC met on March 22, 2001 to consider a request to reaffirm the data waivers. The TOX SAC examined the 1978 Monograph on urea by the FDA Select Committee on GRAS Substances, the HED One Liners, and the 21 CFR Citation 184.1923, which affirms urea as GRAS as a direct human food ingredient. It was noted that the FDA GRAS affirmation was without limitations other than the current good manufacturing practice and that there are no prior sanctions for this chemical. Based on the information presented to the TOX SAC, the Council voted unanimously to affirm the toxicology data waivers and to recommend that no further toxicity studies be required. The affirmed toxicology data waivers are listed in Table 3. A summary of literature studies evaluated for this analysis is provided below.

TABLE 3. HED AFFIRMED TOXICOLOGY DATA WAIVERS FOR UREA

Study Type	Guideline Number
90 Day Oral Feeding Study in Rodents	870.3100
90 Day Oral Feeding Study in Nonrodents	870.3150
21 Day Dermal Toxicity Study	870.3200
90 Day Dermal Toxicity Study	870.3250
90 Day Inhalation Toxicity Study	870.3465
Chronic Feeding Studies in Rodents and Nonrodents	870.4100
Carcinogencity Studies in Two Mammalian Species	870.4200; 870.4300
Developmental Toxicity Studies in Rodents and Nonrodents	870.3700
Multigeneration Reproduction Study in Rodents	870.3800
Battery of Mutagenicity Studies	870.5100; 870.5300; 870.5385; 870.5375; 870.5395
General Metabolism Study	870.7485

3.1.3 Subchronic Toxicity

Urea produced no severe toxicity in dogs injected subcutaneously with 30-40 mL/kg/day of 10% urea solution for 45 days. With plasma levels ranging from 200-700 mg/100 mL (10-30 fold above normal), the only clinical symptoms observed were drowsiness and diuresis. Necropsy indicated no adverse organ pathology.

Rats fed rations containing 2 to 25 percent urea (2- 25 g/kg body weight daily) for periods up to 190 days showed systemic toxicities. Rats receiving14 percent urea in their diet and deprived of water died within a few days. (The lethal dose (LD_{50}) for an oral exposure in rats was 14.5 g/kg (14% urea) which would be equivalent to a two pound ingestion of urea by an average size adult human.) Animals allowed water survived for 20 to 76 days when fed the 20 percent urea supplement and 12 days when fed the 25 percent urea supplement. Weight loss and suppression of sexual function were observed at the lower levels of urea ingestion. Anemia and renal hypertrophy were also observed in some these animals. It is difficult to interpret these findings, however, because of the number of rats tested per treatment group was small (often 1 to 3) and no data were given on the actual food intake. The extreme weight loss observed in rats suggests that starvation was most likely the result of decreased palatability of the animal feed containing urea.

Clinical data on humans indicates that uremia (severe gastrointestinal, cardiovascular, mental and neurologic toxicity) does not occur even at relatively high blood concentrations of urea. Severe forms of uremia are not manifested in dialysis patients with blood urea concentrations above 300 mg/100 mL. (Normal human blood plasma concentration ranges from 20 to 30 mg/100 mL.) High blood concentrations of 181 to 600 mg urea/100 mL were maintained by intermittent dialysis in three patients suffering from advanced renal failure for periods of 7 to 90 days. When the urea concentration was kept below 300 mg/100 mL, no adverse effects were noted although this level is about 10 times greater than normal. Concentrations above 300 mg per 100 mL were associated with malaise, vomiting, bleeding tendency and headache. However, the more severe uremia were not observed. In eight patients with sickle cell disease, 40 to120 g (0.6 to 2.0 g/kg) urea was administered orally in divided doses each day for periods of 3 weeks to 9 months. The blood urea concentrations of the patients approximately doubled during the test periods. While the patients were ingesting urea, there was a slight decrease in blood volume, probably resulting from the chronic osmotic diuresis induced by the urea. The most obvious effects of the urea intake were thirst and diuresis and two patients were unable to complete the study because of nausea and vomiting.

3.1.4 Chronic Toxicity and Carcinogenicity

No toxicities from urea have been reported in humans after chronic exposures. Animal studies provide no evidence of adverse chronic or carcinogenic effects. One year feeding studies in male and female C57B1/6 mice and Fisher 344 rats reported no evidence of treatment-related cancer at doses up to 4.5% of the diet. Slight increases in the incidence of lymphomas occurring in mid-dose female mice, as well as interstitial cell adenomas of the testes occurring in high-dose male rats, were not considered biologically significant in this study. Studies in the susceptible mouse strain (Strain A) also indicate no evidence of urea tumorigenicity. Doses of 10 to 50 mg urea (0.5 - 2.5 g/kg) were injected subcutaneously in Strain A mice on a weekly basis over a period of 11 months. No tumors were evident after 15 months. Weekly intraperitoneal injections of 0.4 g/kg urea administered over a 13 week interval produced no lung adenomas in the mouse strain A.

3.1.5 Developmental and Reproductive Toxicity

In a developmental toxicity study, pregnant Wistar rats receiving a twice-daily dose of 25 g/kg urea by gastric intubation for 14 days produced healthy offspring with no reported evidence of teratogenic effects. A study of pregnant cows that had recovered from urea toxicity, exhibited no effects on reproductive performance nor were the calves affected. These animals were treated acutely with urea (0.44 g/kg) and kept under regular management for 12 months. There was no effect on the number of calves born, birth weight, weaning weight of calves, or rebreeding performance was.

Urea has also been evaluated in monkeys and humans for its ability to induce abortion. In humans, intra-amniotic injection of 80 grams "Ureaphil"/210 mL in 5% dextrose was effective in inducing abortion at 14 weeks without adverse effects to the mother. The mode of action is similar to the hyperosmolar effect of large doses of hypertonic saline and dextrose where a highly localized hyperosmolar solute passes from the amniotic fluid into the fetus causing death. However, such high intrauterine exposures would not occur from environmental exposure to urea. Urea is currently classified by FDA in category C for therapeutic use, "Safety for use during pregnancy has not been established".

3.1.6 Mutagenicity

Several *in vitro* studies have reported that urea is associated with chromosomal aberrations in human leukocytes, hamster fibroblasts and lung cells. All of these studies were conducted with urea concentrations ranging from 50 mM (millimoles) to 8 M. At physiological levels (1mM), urea causes no chromosome effects. However, at concentrations of urea greater than or equal to 50mM, the production of chromosome fragmentation is probably due to a non-specific, hyperosmolarity effect on cell division and not a direct effect of the urea molecule. Sodium phosphate, another normal body fluid constituent also produces chromosomal damage at 50 mM concentrations.

3.1.7 Absorption, Metabolism, and Excretion

Urea is extremely soluble in water and oral doses are rapidly absorbed and distributed through the most body tissues and fluids, in proportion to their water content. The penetration of urea into fatty tissue such as the brain is lower than for most other tissues. Also, the colon has been reported to be relatively impermeable to urea. A study of pregnant rats injected subcutaneously with urea indicates that urea penetrates rapidly into maternal tissues and organs and also readily passes through the placenta. The absorption of urea is very rapid in humans also. In one study, blood urea concentration was generally found to peak within 30 minutes after oral administration.

Urea is a normal human body constituent and is constantly being produced during amino acid

and protein metabolism. Urea is formed metabolically through a cyclic mechanism. Free ammonia arising from the oxidative deamination of glutamate in liver mitochondria combines with carbon dioxide to form carbamoyl phosphate. The carbamoyl group is transferred to ornithine to form citrilluline, which in turn reacts with aspartate to produce arginosuccinate. This is hydrolysed enzymatically to liberate free arginine and fumarate. The fumarate returns to the pool of tricarboxylic acid cycle intermediates, while the arginine is cleaved by arginase to produce urea and ornithine. A 70 kg adult excretes urea in the amount of 25-30 g/day (350-420 mg/kg/day). The ability of the kidney to remove urea from the blood provides one method of assessing renal function. Genetic deficiency of any of the enzymes required in the urea cycle produces protein intolerance, elevated amounts of blood ammonia, metabolic disturbances, neurological symptoms and brain damage.

Urea has long been used as a dietary supplement for ruminants as a source of nitrogen for protein synthesis. Bacterial action in the gastrointestinal tract, particularly in the colon, produces ammonia which is absorbed and mixed with the metabolic pool of nitrogen. Urea nitrogen can also contribute part of the amino acid requirements in humans. Utilization of urea nitrogen has been demonstrated both in malnourished children and adults.

3.1.8 Therapeutic Uses

Urea is approved for several therapeutic uses in humans with relatively few toxicities. Urea is used primarily as an osmotic agent for inducing diuresis and reducing intraoccular and intracranial pressure (Ureaphil, 30% urea solution). Intravenous doses of 1-1.5 g/kg urea (30% urea solution) are considered optimal for neurosurgical procedures with no adverse effects. Urea has also been used as a topical anesthetic for the treatment of mouth and throat inflammation (10-15% urea gel, liquid or solution), to debride necrotic and infected tissues, i.e. fingernails and toenails (2-40% formulations). It is also used in the treatment of sickle-cell anemia and to ammoniate dentrifices as well as a basic ingredient in the synthesis of medically important compounds such as barbiturates and urethanes.

3.2 FQPA Considerations

The Office of Pesticide Program's Inert Ingrediant Focus Group (IIFG) evaluated the available hazard and exposure data for urea on November 6, 2001. The IIFG concluded that the data provide no indication of increased sensitivity of infants and children from exposure to urea. Therefore, the FQPA 10x factor to account for enhanced sensitivity of infants and children can be removed. (11/6/01 IIFG Decision Memo, C. Boyle & K. Leifer)

3.3 Dose Response Assessment

Establishment of toxicity endpoints for use in risk assessment was not required for urea due to its low intrinsic hazard.

4.0 EXPOSURE ASSESSMENT

Based on the hazard assessment of urea, exposures to this compound resulting from reasonably anticipated patterns of usage present no unreasonable adverse human health effects.
Given the low toxicity of this compound, a more detailed assessment of risks resulting from exposure to urea used as a frost protectant is unnecessary.

5.0 ENVIRONMENTAL FATE AND TRANSPORT

The Environmental Fate and Effects Division (EFED) has no fate data for urea. Available data from literature reviews show that urea degrades rapidly in most soils. In general, it is rapidly hydrolyzed to ammonium through soil urease activity. In various soils, the hydrolysis may near completion within 24 hrs; however, the rate of hydrolysis can be much slower depending upon soil type, moisture content, and urea formulation. Soil adsorption studies have demonstrated that urea adsorbs very weakly to soil; therefore, leaching is possible. Ultimate urea degradation produces ammonia and CO_2 as volatile products. Biodegradation is expected to be the major fate process in the aquatic ecosystem. Various screening studies have demonstrated that urea can biodegrade readily with the release of CO_2 and ammonia. The rate of biodegradation generally decreases with decreasing temperatures; under cold winter-like conditions, biodegradation may be relatively slow (0-6% per day). The presence of naturally-occurring phytoplankton increases the degradation rate because phytoplankton use urea as a nitrogen source and because urea is decomposed by phytoplankton photosynthesis; in phytoplankton-rich waters, degradation occurs much faster in sunlight than in the dark. Abiotic hydrolysis of urea occurs very slowly in relation to biotic hydrolysis. Abiotic hydrolysis yields ammonium carbamate which decomposes to form CO_2 and ammonia; the enzyme urease catalyzes urea hydrolysis. (D277581, Ibrahim Abdel-Saheb, 10/11/01)

At the present time, the EFED has no monitoring data on the concentrations of urea in surface water. EFED did provide Tier I estimated drinking water concentrations for urea use on citrus (D277581). However, because of the low toxicity of urea and the subsequent lack of toxicity endpoints for use in risk assessment, HED did not calculate drinking water levels of comparison (DWLOCs) for urea.

6.0 CONCLUSION - Recommended Exemption from Tolerance Requirement

Based upon reevaluation of existing data, HED believes there is sufficient basis for granting a permanent exemption from the requirement of a tolerance for residues of the frost protectant urea when used before harvest in the production of the raw agricultural commodities currently listed under 40 CFR §180.1117.